P/00/001 28/5/91
Section 29

AUSTRALIA

Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the persons identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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[70] Nominated Person: ADIR ET COMPAGNIE

Address: 1 RUE CARLE HEBERT, 92415 COURBEVOIE CEDEX, FRANCE

[54] Invention Title: NEW SUBSTITUTED INDOLES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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Attorney Code: WM

BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
9305686	FRANCE	FR	12 MAY 1993

Basic Applicant(s): ADIR ET COMPAGNIE

Drawing number recommended to accompany the abstract .....

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....
Louis C. Gebhardt
Registered Patent Attorney

DATED this 10th day of May 1994.

M055790 100594

AU9461974

(12) PATENT ABSTRACT (11) Document No. AU-A-61974/94
(19) AUSTRALIAN PATENT OFFICE

(54) Title
NEW SUBSTITUTED INDOLES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(51)[5] International Patent Classification(s)
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ADIR ET COMPAGNIE

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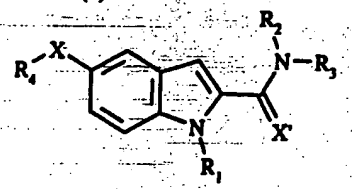
(57) Claim

1. Compounds of formula (I):



(I)

wherein :

- R_1 is selected from hydrogen and a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms,

- R_2 is selected from hydrogen, a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 12 carbon atoms, and a cycloaliphatic radical containing from 3 to 8 carbon atoms that is optionally substituted by one or more R_5 groups,

- R_3 is selected from :

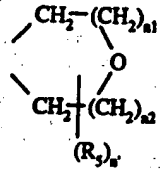
* a cycloaliphatic radical containing from 3 to 8 carbon atoms,
* an aryl radical selected from the phenyl radical and the naphthyl radical,
* and a heteroaryl radical selected from the radicals furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, indolyl, benzofuranyl, benzo[b]thienyl, and benzimidazolyl,

.../2

it being possible for each of the alkyl, cycloaliphatic, aryl, aralkyl, heterocyclyl and heteroaryl radicals optionally to be substituted by one or more R_5 groups,

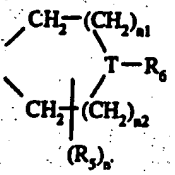
- or R_2 and R_3, together with the nitrogen atom to which they are attached, form a radical selected from :

a) the radical of formula (a) :



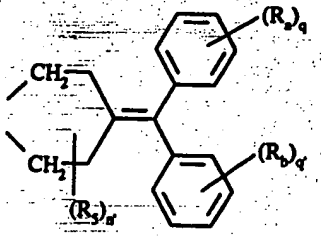
(a)

b) the radical of formula (b) :



(b)

c) and the radical of formula (c) :



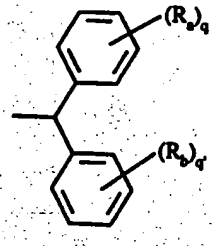
(c)

- R_4 is selected from hydrogen, a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms, an aryl and heteroaryl radical selected from those described for the radical R_3, an aralky radical and a heteroarylalkyl radical in which the aryl and heteroaryl radicals are as defined above and the alkyl chain contains from 1 to 5 carbon atoms in straight or branched chain, each optionally being substituted by one or more R_5 groups,

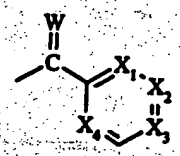
- R_5 is selected from a halogen atom and a hydroxy, nitro, cyano, alkyl, alkoxy, acyl, carboxy, alkoxycarbonyl, carboxamido, haloalkyl, amino, alkylamino and dialkylamino group, the alkyl chains of the alkyl, alkoxy, acyl, alkoxycarbonyl, carbamoyl, haloalkyl, alkylamino and dialkylamino groups containing from 1 to 5 carbon atoms in straight or branched chain,

- R_6 represents either hydrogen or a radical selected from :

α) the radical



β) and the radical



- X_1, X_2, X_3 and X_4 each represents, independently of the others, nitrogen, the group CH or the group C-Ra,

- Ra and Rb, which are the same or different, are each selected, independently of the other, from a halogen atom and a hydroxy, alkyl, alkoxy and haloalkyl radical each containing from 1 to 5 carbon atoms in straight or branched chain,

- T is selected from a CH group and a nitrogen atom,

- W is selected from O and H_2,

- n_1 is 0, 1, 2 or 3,

- n_2, depending on n_1, is an integer of from 0 to $(3-n_1)$ inclusive,

- n' is a value from 0 to (n_1+n_2+2) (inclusive),

- m is selected from 0, 1, 2, 3 and 4,

- q and q' are each, independently of the other, a value of from 0 to 5 (inclusive),

- X is selected from O and S,

and

- X' is selected from O, S and H_2,

with the following provisos:

- when R_2 represents hydrogen R_3 cannot represent a phenyl radical substituted in the 4 position by an oxy-2-hydroxy (or alkoxy)-3-aminopropyl chain, nor a phenyl radical substituted in the 2 position by a carboxy radical,

- when R_2 represents hydrogen, X represents sulphur and R_4 represents a para-nitrophenyl radical, R_3 cannot represent an optionally substituted aryl radical,

- when R_2 and R_3, together with the nitrogen atom to which they are attached, form a radical selected from those of formulae (a), (b) and (c) as defined hereinbefore, then -X-R_4 cannot represent a -O-alkyl as defined hereinbefore,

their possible stereoisomers, N-oxides and addition salts with a pharmaceutically acceptable acid or base.

12. Pharmaceutical compositions according to claim 11 which exert an antioxidant activity specific to LDLs and membrane lipids and are useful in the treatment or prevention of disorders resulting from or associated with such peroxidation phenomena and, especially, cerebral, renal or cardiac ischaemic disorders and metabolic disorders, notably atheroma and arteriosclerosis, as well as inflammation.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title: NEW SUBSTITUTED INDOLES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

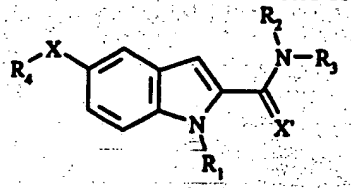
The following statement is a full description of this invention, including the best method of performing it known to us :-

The present invention relates to new substituted indoles, a process for their preparation and pharmaceutical compositions containing them.

The literature provides some examples of indoles substituted in the 2 position : the work by E. Fernandez-Alvarez *et al.*, in the patent ES-2013391, discloses the preparation of allenic and acetylenic compounds of 2-aminomethyl-5-methoxyindoles starting from the correspondin carboxamides. In Eur. J. Med. Chem. 25, 257-265 (1990), the same authors demonstrate, f those same compounds, their inhibiting activity in relation to forms A and B of monoamine oxidase (MAO).

The Applicant has discovered that new indoles substituted in the 2 position have very valuable pharmacological properties based on their specific inhibiting ability with respect to the oxidation of human LDLs (Low Density Lipoproteins) and membrane lipids.

More specifically, the invention relates to new indoles of the general formula (I)



(I)

wherein :

- R_1 is selected from hydrogen and a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms,

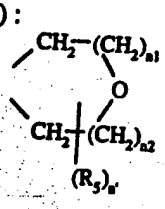
- R_2 is selected from hydrogen, a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 12 carbon atoms, and a cycloaliphatic radical containing from 3 to 8 carbon atoms that is optionally substituted by one or more R_5 groups,

- R_3 is selected from :
  - a cycloaliphatic radical containing from 3 to 8 carbon atoms,
  - an aryl radical selected from the phenyl radical and the naphthyl radical,
  - and a heteroaryl radical selected from the radicals furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, indolyl, benzofuranyl, benzo[b]thienyl, and benzimidazolyl,

it being possible for each of the cycloaliphatic, aryl, and heteroaryl radicals optionally to be substituted by one or more R_5 groups,

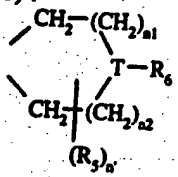
- or R_2 and R_3, together with the nitrogen atom to which they are attached, form a radical selected from :

a) the radical of formula (a) :



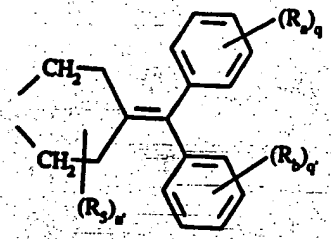
(a)

b) the radical of formula (b) :



(b)

c) and the radical of formula (c) :



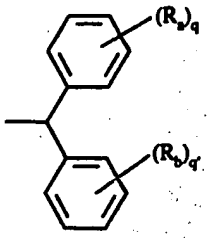
(c)

- R_4 is selected from hydrogen, a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms, an aryl and heteroaryl radical selected from those described for the radical R_3, an aralky radical and a heteroarylalkyl radical in which the aryl and heteroaryl radicals are as defined above and the alkyl chain contains from 1 to 5 carbon atoms in straight or branched chain, each optionally being substituted by one or more R_5 groups,

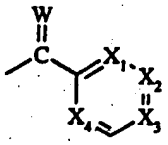
- R_5 is selected from a halogen atom and a hydroxy, nitro, cyano, alkyl, alkoxy, acyl, carboxy, alkoxycarbonyl, carboxamido, haloalkyl, amino, alkylamino and dialkylamino group, the alkyl chains of the alkyl, alkoxy, acyl, alkoxycarbonyl, carbamoyl, haloalkyl, alkylamino and dialkylamino groups containing from 1 to 5 carbon atoms in straight or branched chain,

- R_6 represents either hydrogen or a radical selected from :

α) the radical



β) and the radical



- X_1, X_2, X_3 and X_4 each represents, independently of the others, nitrogen, the group CH or the group C-R_a,

- R_a and R_b, which are the same or different, are each selected, independently of the other, from a halogen atom and a hydroxy, alkyl, alkoxy and haloalkyl radical each containing from 1 to 5 carbon atoms in straight or branched chain,

- T is selected from a CH group and a nitrogen atom,

- W is selected from O and H_2,

- n_1 is 0, 1, 2 or 3,

- n_2, depending on n_1, is an integer of from 0 to $(3-n_1)$ inclusive,

- n' is a value from 0 to (n_1+n_2+2) (inclusive),

- m is selected from 0, 1, 2, 3 and 4,

- q and q' are each, independently of the other, a value of from 0 to 5 (inclusive),

- X is selected from O and S,
and
- X' is selected from O, S and H_2,

with the following provisos:

- when R_2 represents hydrogen R_3 cannot represent a phenyl radical substituted in the 4 position by an oxy-2-hydroxy (or alkoxy)-3-aminopropyl chain, nor a phenyl radical substituted in the 2 position by a carboxy radical,

- when R_2 represents hydrogen, X represents sulphur and R_4 represents a para-nitrophenyl radical, R_3 cannot represent an optionally substituted aryl radical,

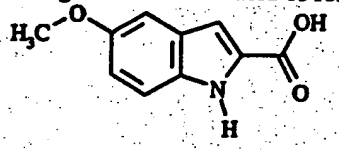
- when R_2 and R_3, together with the nitrogen atom to which they are attached, form a radical selected from those of formulae (a), (b) and (c) as defined hereinbefore, then $-X-R_4$ cannot represent a -O-alkyl as defined hereinbefore,

their possible stereoisomers, N-oxides and addition salts with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids that may be used for the formation of an addition salt with the compounds of the invention there may be mentioned, as non-limiting examples, hydrochloric, phosphoric, sulphuric, tartric, citric, maleic, fumaric, alkylsulphonic and camphoric acid.

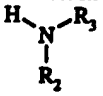
Among the pharmaceutically acceptable bases that may be used for the formation of an addition salt with the compounds of the invention there may be mentioned, as non-limiting examples, sodium or potassium hydroxide, diethylamine, triethylamine, ethanolamine, diethanolamine, arginine and lysine.

The invention relates also to a process for the preparation of compounds of formula (I), characterised in that the starting material is the acid of formula (II):



(II)

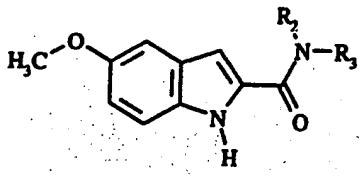
which is converted into the corresponding acyl chloride by an appropriate reagent, for example phosphorus pentachloride, in a polar solvent, for example ether, and then subjected to the action of a secondary amine of formula (III) :



(III)

wherein R_2 and R_3 are as defined for formula (I),

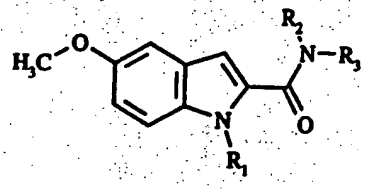
in order to obtain the amide of formula (IV) :



(IV)

wherein R_2 and R_3 are as defined above,

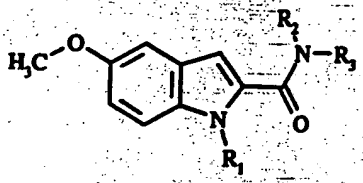
of which the indole nitrogen atom is optionally alkylated by the successive action of a deprotonating agent, such as sodium hydride, and an alkylating agent of formula B-R'$_1$ in which B represents a halogen atom or a sulphate group and R'$_1$ represents a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms, in an appropriate solvent, such as dimethylformamide, to yield a compound of formula (IV') :



(IV')

wherein R'$_1$, R_2 and R_3 are as defined hereinbefore,

the totality of the compounds of formula (IV) and (IV') forming the totality of the compounds of formula (Va) :

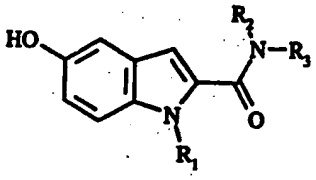


(Va)

wherein R_1, R_2 and R_3 are as defined hereinbefore,

a particular instance of compounds of formula (I) in which -X-R_4 represents the methoxy group,

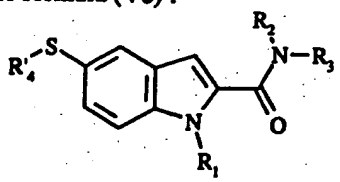
it being possible for the compounds of formula (Va), if desired, to be subjected to an O-demethylation according to the method described by Fujita *et al.* (J. Org. Chem., 45, 4275, (1980)) by the action of a Lewis acid and an alkylthiol, to obtain the compounds of formula (Vb):



(Vb)

wherein R_1, R_2 and R_3 are as defined hereinbefore,

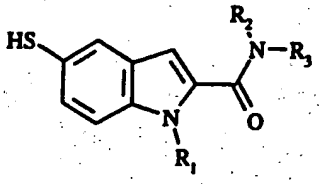
that reaction likewise leading, according to the operating conditions and by using an alkylthiol of the formula R'4-SH in which R'4 has all the possible meanings of R_4 with the exception of hydrogen, to compounds of formula (Vc) :



(Vc)

wherein the substituents R_1, R_2, R_3 and R'4 are as defined hereinbefore,

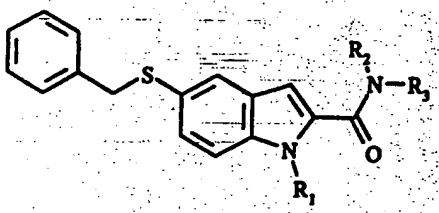
the compounds of formula (Vd) :



(Vd)

wherein R_1, R_2 and R_3 are as defined hereinbefore

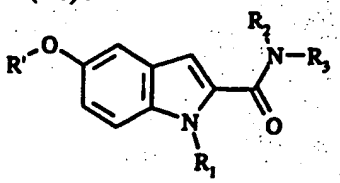
being obtained by debenzylation, by chemical or catalytic reduction, of compounds of formula (Vc') :



(Vc')

a particular instance of compounds of formula (Vc) wherein R'4 represents a benzyl radical,

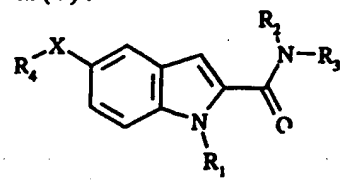
the compounds of formula (Vb) optionally being subjected to a conventional etherification to yield compounds of formula (Ve) :



(Ve)

wherein R_1, R_2 and R_3 are as defined hereinbefore and R' represents an optionally substituted straight-chain or branched alkyl radical containing from 2 to 5 carbon atoms, or an aryl, aralkyl, heteroaryl or heteroarylalkyl radical selected from those described for R_4.

the totality of the compounds of formulae (Va), (Vb), (Vc), (Vd) and (Ve) forming the totality of the compounds of formula (V) :

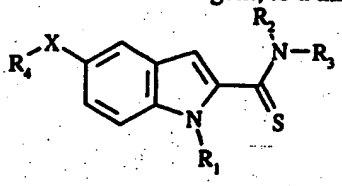


(V)

wherein X, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

a particular instance of compounds of formula (I) wherein X' represents oxygen, which are either :

- converted, by treatment with Lawesson's reagent, to a thioamide of formula (V') :

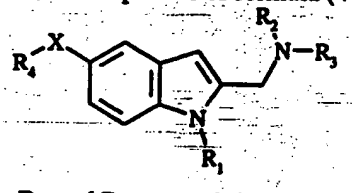


(V')

wherein X, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

a particular instance of compounds of formula (I) wherein X' represents sulphur,

- or reduced, using a reducing agent, such as lithium aluminium hydride, in an anhydrous solvent, such as diethyl ether, to compounds of formula (V") :



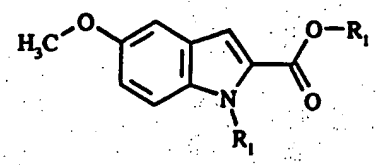
(V")

wherein X, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

a particular instance of compounds of formula (I) wherein X' represents an H_2 group,

the totality of the compounds of formulae (V), (V') and (V") forming the totality of the compounds of formula (I), which are purified and optionally separated into their stereoisomers by a conventional method of separation and, if desired, converted into their pharmaceutically acceptable addition salts with an acid or a base.

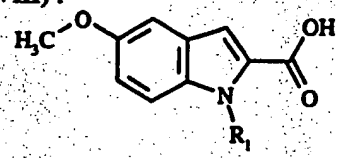
The alkylation of the nitrogen atom described for the compounds of formula (IV) can also be carried out directly on the starting compound of formula (II). In that case, the compound obtained is the compound of formula (VII) :



(VII)

wherein R_1 is as defined hereinbefore,

which is then hydrolysed by the action of a base, such as potassium hydroxide, to yield the compound of formula (VIII) :

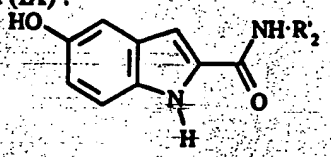


(VIII)

wherein R_1 is as defined hereinbefore,

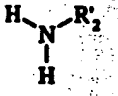
which is then treated in an analogous manner to the compound of formula (II) to yield the compound of formula (I).

The compounds of formula (IX) :



(IX)

a particular instance of compounds of formula (I) wherein R_1 represents hydrogen, R'_2 represents an aryl radical as defined hereinbefore, R_3 and R_4 each represents hydrogen and X and X' each represents oxygen, are obtained from 5-hydroxyindole-2-carboxylic acid, which is converted into its corresponding acyl chloride by the action of thionyl chloride, the acyl chloride then being treated with an amine of formula (X) :



(X)

wherein R'_2 is as defined hereinbefore.

The compounds of the present invention surprisingly exhibit very significant anti-oxidant properties. Pharmacological studies have in particular demonstrated that those compounds have remarkable protecting activities specific to the peroxidation of low-density lipoproteins (LDLs) and membrane lipids.

The compounds of the invention have also exhibited an anti-inflammatory activity and have a platelet anti-aggregation activity.

The compounds of the invention thus have a new and especially beneficial activity in

disorders involving peroxidation of the membrane lipids. The new compounds can thus be used in the treatment or prevention of disorders resulting from or associated with such peroxidation phenomena and, especially, cerebral, renal or cardiac ischaemic disorders and metabolic disorders notably atheroma and arteriosclerosis, as well as inflammation.

The present invention relates also to pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable addition salt thereof with an acid or a base, alone or in combination with one or more inert non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned more especially those which are suitable for oral, parenteral, nasal, rectal, perlingual, ocular or pulmonary administration and, in particular, injectable preparations, aerosols, eye or nose drops, tablets, film-coated tablets, dragées, soft gelatin capsules, hard gelatin capsules, creams, ointments, dermal gels, suppositories...

The dosage varies in accordance with the age and weight of the patient, the route of administration, the nature of the disorder and any associated treatments, and ranges from 0.5 mg to 2 g per 24 hours.

The following Examples illustrate the invention without in any way limiting it.

The starting materials are readily available or are prepared by known operating methods.

EXAMPLE 1 : N-Methyl-N-phenyl-(5-methoxyindol-2-yl)carboxamide

1 g (5.23 mmol) of 5-methoxyindole-2-carboxylic acid is added to 60 ml of anhydrous diethyl ether, then 1.64 g (7.85 mmol) of phosphorus pentachloride. When the solution has become clear, the solvent is evaporated off *in vacuo*. The residue is taken up in 50 ml of anhydrous ether, which is subsequently evaporated off, and then the same operation is carried out twice with 50 ml of trichloromethane. The precipitate obtained is dissolved again in 50 ml of anhydrous ether. The solution is cooled to 0°C in an ice bath, and then 1.12 g (10.46 mmol) of N-methylaniline in 15 ml of dry dioxane are added dropwise. The solution is stirred for one night at room temperature, the solvent is then evaporated off *in vacuo*, and the precipitate is taken up in 50 ml of trichloromethane, washed with a dilute solution of hydrochloric acid (1N), and then four times with water. The organic phase is then dried over magnesium sulphate and the solvent is subsequently evaporated off *in vacuo*. The precipitate obtained is then washed several times with petroleum ether and recrystallised from ethanol.
Yield : 86 %.

Melting point : 194°C.

EXAMPLE 2 : N-Methyl-N-phenyl-(5-methoxy-1-methylindol-2-yl)carboxamide

Under an inert atmosphere, 174 mg (7.6 mmol) of sodium hydride are added to 10 ml of dimethylformamide cooled to 0°C. 1 g (3.8 mmol) of the compound obtained in Example 1 are then added dropwise. After returning to room temperature, the mixture is stirred for a further 5 minutes before 1.43 g (11.4 mmol) of dimethyl sulphate is slowly added. After 1 1/2 hours, the solution, which has become clear, is hydrolysed and treated with a 10 % aqueous ammonium hydroxide solution, and then extracted with diethyl ether. After customary treatment of the organic phase, the expected product is recrystallised from a mixture of ethyl acetate/petroleum ether (50/50).

Yield : 84 %.

Melting point : 94°C.

EXAMPLE 3 : N-Methyl-N-phenyl-(5-hydroxy-1-methylindol-2-yl)carboxamide

500 mg (1.8 mmol) of the compound obtained in Example 2, dissolved in 5 ml of methylene chloride which has beforehand been distilled over phosphorus pentoxide, are added to a mixture, cooled to 0°C, of 360 mg (2.7 mmol) of aluminium chloride and 2.2 g (36 mmol) of ethanethiol. After the mixture has been stirred for 1 hour at 0°C, 1.5 equivalents of aluminium chloride and 20 equivalents of ethanethiol are added. After 2 hours at 0°C, the mixture is poured onto ice and acidified to pH 2 with a 1N hydrochloric acid solution. After extraction with dichloromethane, treatment of the organic phase, and purification by chromatography on a silica column, the expected phenolic indole is obtained.

Yield : 50 %.

Melting point : 139°C.

EXAMPLE 4 : N-Phenyl-(5-methoxy-1-methylindol-2-yl)carboxamide

500 mg (21 mmol) of sodium hydride are added to 10 ml of dimethylformamide at 0°C, then 1 g (5.23 mmol) of 5-methoxyindole-2-carboxylic acid dissolved in 20 ml of dimethylformamide. After returning to room temperature, the mixture is stirred for a further 5 minutes, then 2.3 g (18.3 mmol) of dimethyl sulphate are added. The reaction mixture is subsequently hydrolysed, treated with a 10 % ammonium hydroxide solution and then

extracted with ether. After customary treatment of the organic phase, a solid corresponding to methyl 5-methoxy-1-methylindole-2-carboxylate is obtained which is used crude for the hydrolysis. For that purpose, 1 g (4.9 mmol) of the ester in 30 ml of a 10 % solution of potassium hydroxide in ethanol is heated at reflux for 1 hour and then cooled. After extraction with ether, acidification with a 10 % hydrochloric acid solution and customary treatment of the organic phase, the solid obtained is treated with aniline as described in Example 1. The expected amide is recrystallised from ethanol.

Yield : 70 %.

Melting point : 200°C.

EXAMPLE 5 : N-Phenyl-(5-hydroxy-1-methylindol-2-yl)carboxamide

500 mg (1.9 mmol) of the compound obtained in Example 4, which have beforehand been dissolved in 5 ml of methylene chloride, are slowly added to a mixture, cooled to 0°C, of 712 mg (2.84 mmol) of aluminium bromide and 4.2 g (37.9 mmol) of thiophenol. At two intervals of half an hour there are then added twice 1.5 equivalents of aluminium bromide and 20 equivalents of thiophenol. After having been stirred for a total of 2 hours at 0°C, the solution is poured onto ice, acidified with 1N hydrochloric acid to pH 2 and then extracted with dichloromethane. After customary treatment of the organic phase, the crude product is purified by chromatography on a silica column.

Yield : 44 %.

Melting point : 195°C.

EXAMPLE 6 : N-Phenyl-(5-ethylthio-1-methylindol-2-yl)carboxamide

500 mg (1.9 mmol) of the compound obtained in Example 4, which have beforehand been dissolved in 5 ml of methylene chloride distilled over phosphorus pentoxide, are added dropwise to a mixture, cooled to 0°C, of 380 mg (2.84 mmol) of aluminium chloride and 2.3 g (37.9 mmol) of ethanethiol. After the mixture has been stirred for 1 hour at 0°C, 1.5 equivalents of aluminium chloride and 20 equivalents of ethanethiol are added. The mixture is stirred for a further hour at 0°C, then poured onto ice, treated with 1N hydrochloric acid and subsequently extracted with dichloromethane. After customary treatment of the organic phase and purification of the crude product by chromatography on a silica column, the expected compound is obtained.

Yield : 30 %.

Melting point : 130°C.

Examples 7 and 8 are prepared in accordance with the method of operation described for Example 1 with condensation of the corresponding amine to the desired compound.

EXAMPLE 7 : N-Phenyl-(5-methoxyl. dol-2-yl)carboxamide

Melting point : 191°C.

EXAMPLE 8 : N-(3-Methoxyphenyl)-(5-methoxyindol-2-yl)carboxamide

Melting point : 183°C.

Examples 9 to 12 are prepared in accordance with the method of operation described for Example 1 and O-demethylated according to Example 3.

EXAMPLE 9 : N-Phenyl-(5-hydroxyindol-2-yl)carboxamide

Melting point : 227°C.

EXAMPLE 10 : N-(3,4,5-Trimethoxyphenyl)-(5-hydroxyindol-2-yl)carboxamide

Melting point : 220°C.

EXAMPLE 11 : N-Methyl-N-phenyl-(5-hydroxyindol-2-yl)ca. boxamide

Melting point : 193°C.

EXAMPLE 12 : N-Phenyl-N-(n-octyl)-(5-hydroxyindol-2-yl)carboxamide

Melting point : 160°C.

Examples 13 to 17 are carried out according to the method of operation described for Example 5.

EXAMPLE 13 : N-(3-Chlorophenyl)-(5-hydroxy-1-methylindol-2-yl)carboxamide

Melting point : 187°C.

EXAMPLE 14 : N-Methyl-N-(3-chlorophenyl)-(5-hydroxy-1-methylindol-2-yl)-carboxamide

Melting point : 142°C.

EXAMPLE 15 : N-Methyl-N-(3-trifluoromethylphenyl)-(5-hydroxy-1-methylindol-2-yl)carboxamide

Melting point : 158°C.

EXAMPLE 16 : N-Methyl-N-(3-bromophenyl)-(5-hydroxy-1-methylindol-2-yl)-carboxamide

Melting point : 144°C.

EXAMPLE 17 : N-(n-Butyl)-N-phenyl-(5-hydroxy-1-methylindol-2-yl)carboxamide

Melting point : 150°C.

EXAMPLE 18 : N-Phenyl-N-(n-octyl)-(5-ethylthioindol-2-yl)carboxamide

A compound produced according to a method of operation identical to that described for Example 6.
Melting point : 87°C.

By proceeding in the same manner as for Examples 1, 2 or 3, the following are obtained:

EXAMPLE 19 : **1-Methyl-5-hydroxy-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}carbonylindole**

Melting point : 220°C.

EXAMPLE 20 : **1-Methyl-5-hydroxy-2-[4-(2,3,4-trimethoxybenzyl)piperazin-1-yl]carbonylindole**

EXAMPLE 21 : **1-Methyl-5-hydroxy-2-[4-(4-fluorobenzoyl)piperidin-1-yl]-carbonylindole**

EXAMPLE 22 : **1-Methyl-5-methoxy-2-{4-[bis-(4-fluorophenyl)methylene]piperazin-1-yl}carbonylindole**

EXAMPLE 23 : **N-(Quinol-3-yl)-(5-phenoxy-1-methylindol-2-yl)carboxamide**

EXAMPLE 24 : **1-Methyl-5-benzyloxy-2-[4-(pyrimid-2-yl)piperazin-1-yl]-carbonylindole**

EXAMPLE 25 : **1-Methyl-5-(2-pyridyl)oxy-2-(4-benzylpiperazin-1-yl)carbonylindole**

EXAMPLE 26 : **1-Methyl-5-methoxy-2-(4-phenethylpiperazin-1-yl)carbonylindole**

EXAMPLE 27 : **5-Hydroxy-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}-carbonylindole**

EXAMPLE 28 : N-Cyclohexyl-N-methyl-(5-methoxyindol-2-yl)carboxamide

EXAMPLE 29 : 5-Methoxy-2-(4-methylpiperidino)carbonylindole

EXAMPLE 30 : 5-Benzyloxy-2-{4-[bis-(phenyl)methyl]piperidino}carbonylindole

EXAMPLE 31 : N-Methyl-N-(pyrid-2-yl)-(5-methoxyindol-2-yl)carboxamide

EXAMPLE 32 : 5-Methoxy-2-(4-n-propylpiperazin-1-yl)carbonylindole

EXAMPLE 33 : 5-(2,6-Dimethylpyrid-4-yl)-2-[4-(4-fluorobenzoyl)piperazin-1-yl]-carbonylindole

EXAMPLE 34 : 5-Benzyloxy-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}-carbonylindole

EXAMPLE 35 : 5-Hydroxy-2-[4-(2,3,4-trimethoxybenzyl)piperazin-1-yl]-carbonylindole

Melting point : 181°C.

The following Examples are prepared according to the method of operation described for Example 6.

EXAMPLE 36 : 1-Ethyl-5-ethylthio-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}carbonylindole

EXAMPLE 37 : 1-Methyl-5-methylthio-2-[4-(phenyl)piperazin-1-yl]carbonylindole

EXAMPLE 38 : N-Phenyl-N-(n-butyl)-(5-benzylthioindol-2-yl)carboxamide

EXAMPLE 39 : N-Benzyl-N-methyl-(5-ethylthioindol-2-yl)carboxamide

EXAMPLE 40 : 5-Benzylthio-2-[4-(4-fluorophenyl)piperazin-1-yl]carbonylindole

EXAMPLE 41 : N-(n-Butyl)-N-phenyl-(5-hydroxy-1-methylindol-2-yl)methylamine

2 mmols of the compound obtained in Example 17 are heated at reflux under a nitrogen atmosphere in the presence of 5 mmol of lithium aluminium hydride in 35 cm^3 of diethyl ether. After cooling, hydrolysis, elimination of insoluble mineral material by filtration and drying over sodium sulphate, the crude product is purified by chromatography on a silica column.
Yield : 75 %.

Using an identical method of operation, starting from the appropriate carboxamides, the following amines are obtained:

EXAMPLE 42 : 1-Methyl-5-hydroxy-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}methylindole

The compound is obtained starting from the compound of Example 19.

EXAMPLE 43 : 1-Methyl-5-methoxy-2-(4-phenethylpiperazin-1-yl)methylindole

The compound is obtained starting from the compound of Example 26.

EXAMPLE 44 : N-(n-Butyl)-N-phenyl-(5-hydroxy-1-methylindol-2-yl)thiocarbonylindole

17 mmols of the compound of Example 17 are dissolved in 125 cm^3 of anhydrous toluene. 10.2 mmols of Lawesson's reagent are added and the whole is heated at reflux for 6 hours.

After evaporation of the solvent and purification on a silica column, the title compound is obtained.
Yield : 90 %.

The following are obtained in the same manner:

EXAMPLE 45 : 1-Methyl-5-hydroxy-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}thiocarbonylindole

The compound is obtained starting from the compound of Example 19.

EXAMPLE 46 : 1-Methyl-5-methoxy-2-(4-phenethylpiperazin-1-yl)thiocarbonylindole

The compound is obtained starting from the compound of Example 26.

EXAMPLE 47 : N-(n-Hexyl)-N-phenyl-(5-hydroxyindol-2-yl)carboxamide

The compound is obtained in accordance with the method of operation described in Example 12.
Melting point : 164°C.

EXAMPLE 48 : N-(n-Hexyl)-N-phenyl-(5-hydroxy-1-methylindol-2-yl)carboxamide

The compound is obtained in accordance with the method of operation described in Example 17.
Melting point : 90°C.

EXAMPLE 49 : 5-Hydroxy-1-methyl-{4-[bis-(4-fluorophenyl)methylene]piperidin-1-yl}carbonylindole

The compound is obtained in accordance with the method of operation described in Example 19.

PHARMACOLOGICAL STUDY

Example A : Study of the protective activity against LDL oxidation

The capacity of the compounds of the invention to decrease the proportions of oxidised LDLs was measured in the following manner : incubation of combinations of native human LDLs, a Cu^{2+} free radical generator, and the compounds to be tested is carried out for 24 hours. The results are obtained after analysis of the mixture by a high performance chromatography technique : FPLC (Fast Protein Liquid Chromatography). The protective activity of the tested compound is determined after comparing the resulting chromatogram with that of the positive control used as reference : probucol. It appears clearly that the compounds of the invention have a very significant protective activity. As a comparison, at a concentration of 10^{-5} M, the level of protection obtained for the compounds of the invention surpasses that of probucol. That is true especially of the compound described in Example 17, which has the capacity to provide almost total protection against an LDL oxidant system.

Example B : Study of the protective activity against LDL oxidation (determination of malonic dialdehyde)

Purified LDLs are incubated in the presence of copper sulphate at a concentration of 5.10^{-5} M in the absence or presence of the compounds being studied. The activity of the tested products is evaluated by calculating the concentration that reduces the production of malonic dialdehyde (MDA) by 50 % (IC_{50}) compared with control experiments carried out in the absence of product. The compounds of the invention are remarkably active in that test, with IC_{50}s (about 10^{-7} M) very considerably lower than those determined for probucol.

Example C : *Ex vivo* study in Watanabe rabbits

Watanabe rabbits were treated once per day by the oral route either with the carrier (control group) or the compounds of the invention at the dose of 50 mg/kg/day for 3 days. On day 3, 3 hours after the last treatment the animals are sacrificed and the blood is collected under ethylenediaminetetraacetic acid (EDTA). The LDLs (Low Density Lipoproteins) are purified by ultracentrifugation and subjected to oxidation by copper sulphate ($5x10^{-6}$M). The lipid peroxidation of the LDLs is evaluated after different periods of incubation (from 2 to 48

hours) with copper sulphate by measuring the formation of MDA (malonic dialdehyde).
The compounds of the invention exhibit a significant reduction in the production of MDA compared with the control ($p < 0.001$), thus demonstrating a protective activity against lipid peroxidation *ex vivo* after administration *per os*.

Example D : Study of the antiperoxidant activity

The action of the compounds used in accordance with the invention, which are capable of trapping $^{\bullet}OH$ radicals, was studied on the one hand in the spontaneous peroxidation of lipids and, on the other hand, in peroxidation induced by the system Fe^{2+}-ascorbate (10 mM - 250 mM), in rats' brain homogenates.

a) Study of spontaneous lipid peroxidation

For the measurement of spontaneous lipid peroxidation, rats' brain homogenates are placed in the presence or absence of the compounds to be tested for a period of 60 minutes at 37°C. The reaction is stopped at 0°C and the malonic dialdehyde is measured using thiobarbituric acid. The lipid peroxidation is determined by the substances that react with the thiobarbituric acid expressed in nanomoles of malonic dialdehyde (MDA). The concentrations of the compounds tested that inhibit peroxidation of the substrate by 50 % are calculated. It appeared that the compounds of formula (I) used in accordance with the invention possess a particularly intense antiperoxidant activity since they have an antiperoxidant activity distinctly greater than probucol and vitamin E, which is the natural antioxidant of the human organism.

b) Study of induced lipid peroxidation

For the measurement of induced lipid peroxidation, the methodology is identical to that described above except for the addition to the homogenate of the radical initiator system : Fe^{2+} ascorbate. The reference substances are probucol and vitamin E. The concentrations of the compounds tested that inhibit peroxidation of the substrate by 50 % are calculated. For example, the compound of Example 17 has an IC50 (MDA) equal to 5×10^{-7} M (probucol ratio = 6).

Example E : Study of the anti-inflammatory activity

The measurements are carried out on rabbit granulocytes. The isolated granulocytes are

stimulated *in vitro* by the calcium ionophore (A 23187). The B4 leukotrienes released in the extracellular medium are measured by Radio Immuno Assay (RIA). The results (averages of 3 independent measurements) are expressed as a percentage inhibition compared with the control.

By way of example, the compound of Example 17 exhibits an inhibiting activity of 51 % at 10 mM.

Example F : Study of the antiaggregation activity

In this study, the compounds of the invention (100 mg/ml) were tested with the aim of quantifying their ability to inhibit the maximum non-reversible platelet aggregation (rabbit plasma rich in platelets) induced by sodium arachidonate (50 mg/ml). Thus the minimum active concentration for the compound of Example 17 is 30 mM.

Example G : Pharmaceutical composition : tablets

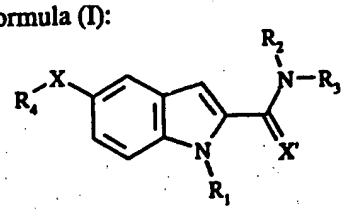
Formulation for the preparation of 1000 50 mg tablets

Compound of Example 1	50 g
wheat starch	15 g
maize starch	15 g
lactose	65 g
magnesium stearate	2 g
silica	1 g
hydroxypropyl cellulose	2 g

CLAIMS

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compounds of formula (I):



(I)

wherein :

- R_1 is selected from hydrogen and a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms,

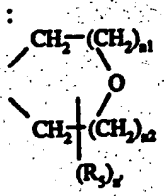
- R_2 is selected from hydrogen, a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 12 carbon atoms, and a cycloaliphatic radical containing from 3 to 8 carbon atoms that is optionally substituted by one or more R_5 groups,

- R_3 is selected from :
  - a cycloaliphatic radical containing from 3 to 8 carbon atoms,
  - an aryl radical selected from the phenyl radical and the naphthyl radical,
  - and a heteroaryl radical selected from the radicals furyl, thienyl, thiazolyl, pyrrolyl, imidazolyl, pyridyl, pyrimidinyl, pyrazolyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, indolyl, benzofuranyl, benzo[b]thienyl, and benzimidazolyl,

  it being possible for each of the alkyl, cycloaliphatic, aryl, aralkyl, heterocyclyl and heteroaryl radicals optionally to be substituted by one or more R_5 groups,

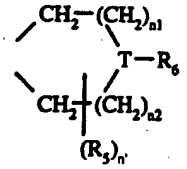
- or R_2 and R_3, together with the nitrogen atom to which they are attached, form a radical selected from :

a) the radical of formula (a) :



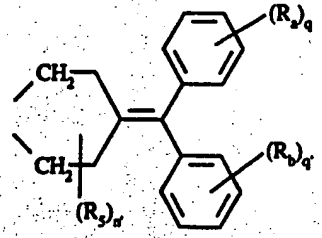
(a)

b) the radical of formula (b) :



(b)

c) and the radical of formula (c) :



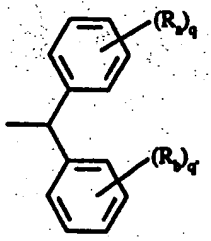
(c)

- R_4 is selected from hydrogen, a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms, an aryl and heteroaryl radical selected from those described for the radical R_3, an aralky radical and a heteroarylalkyl radical in which the aryl and heteroaryl radicals are as defined above and the alkyl chain contains from 1 to 5 carbon atoms in straight or branched chain, each optionally being substituted by one or more R_5 groups,

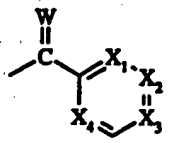
- R_5 is selected from a halogen atom and a hydroxy, nitro, cyano, alkyl, alkoxy, acyl, carboxy, alkoxycarbonyl, carboxamido, haloalkyl, amino, alkylamino and dialkylamino group, the alkyl chains of the alkyl, alkoxy, acyl, alkoxycarbonyl, carbamoyl, haloalkyl, alkylamino and dialkylamino groups containing from 1 to 5 carbon atoms in straight or branched chain,

- R_6 represents either hydrogen or a radical selected from :

α) the radical



β) and the radical



- X_1, X_2, X_3 and X_4 each represents, independently of the others, nitrogen, the group CH or the group C-Ra,

- Ra and Rb, which are the same or different, are each selected, independently of the other, from a halogen atom and a hydroxy, alkyl, alkoxy and haloalkyl radical each containing from 1 to 5 carbon atoms in straight or branched chain,

- T is selected from a CH group and a nitrogen atom,

- W is selected from O and H_2,

- n_1 is 0, 1, 2 or 3,

- n_2, depending on n_1, is an integer of from 0 to $(3-n_1)$ inclusive,

- n' is a value from 0 to (n_1+n_2+2) (inclusive),

- m is selected from 0, 1, 2, 3 and 4,

- q and q' are each, independently of the other, a value of from 0 to 5 (inclusive),

- X is selected from O and S,
and
- X' is selected from O, S and H_2,

with the following provisos:

- when R_2 represents hydrogen R_3 cannot represent a phenyl radical substituted in the 4 position by an oxy-2-hydroxy (or alkoxy)-3-aminopropyl chain, nor a phenyl radical substituted in the 2 position by a carboxy radical,

- when R_2 represents hydrogen, X represents sulphur and R_4 represents a para-nitrophenyl radical, R_3 cannot represent an optionally substituted aryl radical,

- when R_2 and R_3, together with the nitrogen atom to which they are attached, form a radical selected from those of formulae (a), (b) and (c) as defined hereinbefore, then -X-R_4 cannot represent a -O-alkyl as defined hereinbefore,

their possible stereoisomers, N-oxides and addition salts with a pharmaceutically acceptable acid or base.

2. Compounds according to claim 1, in which R_1 represents a hydrogen atom, their stereoisomers, N-oxides and pharmaceutically acceptable addition salts with an acid or a base.

3. Compounds of formula (I) according to claim 1, in which R_1 represents a methyl radical, their stereoisomers, N-oxides and pharmaceutically acceptable addition salts with an acid or a base.

4. Compounds of formula (I) according to claim 1, in which R_4 represents a hydrogen atom, their stereoisomers, N-oxides and pharmaceutically acceptable addition salts with an acid or a base.

5. Compounds of formula (I) according to claim 1, in which R_4 represents a methyl radical, their stereoisomers, N-oxides and pharmaceutically acceptable addition salts with an acid or a base.

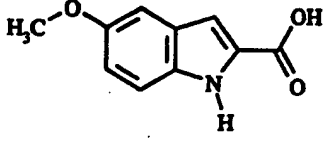
6. Compounds of formula (I) according to claim 1, in which X represents oxygen, their stereoisomers, and pharmaceutically acceptable addition salts with an acid or a base.

7. Compound according to claim 1, which is N-(n-butyl)-N-phenyl-(5-hydroxy-1-methyl-indol-2-yl)carboxamide, and also its pharmaceutically acceptable addition salts with a base.

8. Compound according to claim 1, which is 1-methyl-5-hydroxy-2-{4-[bis-(4-fluorophenyl)methyl]piperazin-1-yl}carbonylindole, and also its pharmaceutically acceptable addition salts with an acid or base.

9. Compound according to claim 1, which is N-(n-hexyl)-N-phenyl-(5-hydroxyindol-2-yl)carboxamide, and also its pharmaceutically acceptable addition salts with a base.

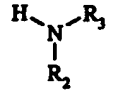
10. Process for the preparation of compounds of formula (I) according to claim 1, characterised in that the starting material is the acid of formula (II):



(II)

which is converted into the corresponding acyl chloride by an appropriate reagent, for

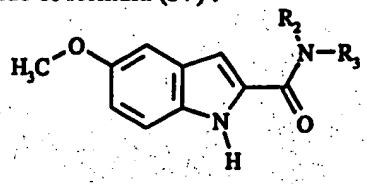
example phosphorus pentachloride, in a polar solvent, for example ether, and then subjected to the action of a secondary amine of formula (III) :



(III)

wherein R_2 and R_3 are as defined for formula (I),

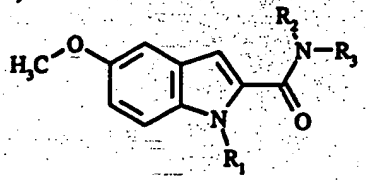
in order to obtain the amide of formula (IV) :



(IV)

wherein R_2 and R_3 are as defined above,

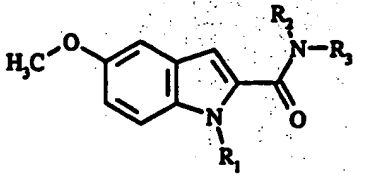
of which the indole nitrogen atom is optionally alkylated by the successive action of a deprotonating agent, such as sodium hydride, and an alkylating agent of formula B-R'_1 in which B represents a halogen atom or a sulphate group and R'_1 represents a straight-chain or branched alkyl radical that is optionally substituted by one or more R_5 groups and contains from 1 to 5 carbon atoms, in an appropriate solvent, such as dimethylformamide, to yield a compound of formula (IV') :



(IV')

wherein R'_1, R_2 and R_3 are as defined hereinbefore,

the totality of the compounds of formula (IV) and (IV') forming the totality of the compounds of formula (Va) :



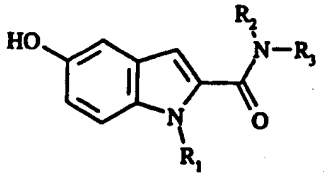
(Va)

wherein R_1, R_2 and R_3 are as defined hereinbefore,

a particular instance of compounds of formula (I) in which -X-R_4 represents the methoxy group,

it being possible for the compounds of formula (Va), if desired, to be subjected to an O-demethylation by the action of a Lewis acid and an alkylthiol, to obtain the compounds of

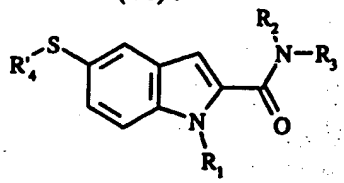
formula (Vb):



(Vb)

wherein R_1, R_2 and R_3 are as defined hereinbefore,

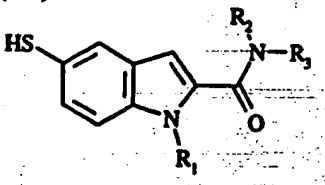
that reaction likewise leading, according to the operating conditions and by using an alkylthiol of the formula R'_4-SH in which R'_4 has all the possible meanings of R_4 with the exception of hydrogen, to compounds of formula (Vc) :



(Vc)

wherein the substituents R_1, R_2, R_3 and R'_4 are as defined hereinbefore,

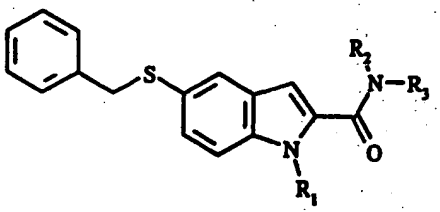
the compounds of formula (Vd) :



(Vd)

wherein R_1, R_2 and R_3 are as defined hereinbefore

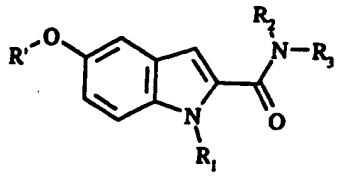
being obtained by debenzylation, by chemical or catalytic reduction, of compounds of formula (Vc') :



(Vc')

a particular instance of compounds of formula (Vc) wherein R'_4 represents a benzyl radical,

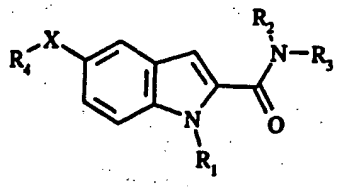
the compounds of formula (Vb) optionally being subjected to a conventional etherification to yield compounds of formula (Ve) :



(Ve)

wherein R_1, R_2 and R_3 are as defined hereinbefore and R' represents an optionally substituted straight-chain or branched alkyl radical containing from 2 to 5 carbon atoms, or an aryl, aralkyl, heteroaryl or heteroarylalkyl radical selected from those described for R_4,

the totality of the compounds of formulae (Va), (Vb), (Vc), (Vd) and (Ve) forming the totality of the compounds of formula (V) :

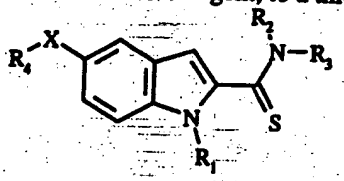


(V)

wherein X, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

a particular instance of compounds of formula (I) wherein X' represents oxygen, which are either :

- converted, by treatment with Lawesson's reagent, to a thioamide of formula (V') :

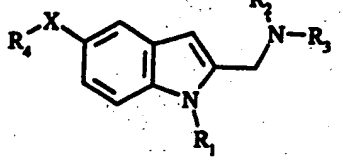


(V')

wherein X, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

a particular instance of compounds of formula (I) wherein X' represents sulphur,

- or reduced, using a reducing agent, such as lithium aluminium hydride, in an anhydrous solvent, such as diethyl ether, to compounds of formula (V") :



(V")

wherein X, R_1, R_2, R_3 and R_4 are as defined hereinbefore,

a particular instance of compounds of formula (I) wherein X' represents an H2 group,

the totality of the compounds of formulae (V), (V') and (V") forming the totality of the compounds of formula (I), which are purified and optionally separated into their stereoisomers by a conventional method of separation and, if desired, converted into their pharmaceutically acceptable addition salts with an acid or a base.

11. Pharmaceutical compositions comprising as active ingredient at least one compound according to any one of claims 1 to 9, alone or in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

12. Pharmaceutical compositions according to claim 11 which exert an antioxidant activity specific to LDLs and membrane lipids and are useful in the treatment or prevention of disorders resulting from or associated with such peroxidation phenomena and, especially, cerebral, renal or cardiac ischaemic disorders and metabolic disorders, notably atheroma and arteriosclerosis, as well as inflammation.

DATED this 10th day of May 1994.

ADIR ET COMPAGNIE

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ABSTRACT

NEW SUBSTITUTED INDOLES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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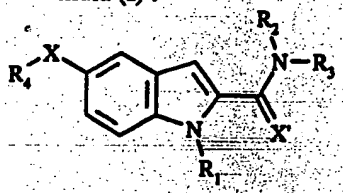
Compounds of the general formula (I) :



(I)

wherein :

- X represents O or S,
- X' represents O, S or H_2,
- and R_1, R_2, R_3 and R_4 are as defined in the description.

Those compounds may be used therapeutically in the treatment or prevention of disorders resulting from or associated with peroxidation phenomena and, especially, cerebral, renal or cardiac ischaemic disorders and metabolic disorders, notably atheroma and arterio-sclerosis, as well as inflammation.